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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/559,676 | 12/07/2005 | Judith A. Boice | 21294P | 1543 |

210 7590 04/16/2009
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| EXAMINER | |
|---|---|
| CLARK, SARA E | |
| ART UNIT | PAPER NUMBER |
| 4121 | |
| MAIL DATE | DELIVERY MODE |
| 04/16/2009 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/559,676 | BOICE ET AL. | |
| | Examiner | Art Unit | |
| | SARA E. CLARK | 4121 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *12 February 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-13,16,18,20 and 22-26* is/are pending in the application.

4a) Of the above claim(s) *13,18 and 20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12,16 and 22-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/7/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

**NON-FINAL REJECTION**

This application is a 35 U.S.C. 371 (national stage) application of PCT/US04/19441, filed 6/16/2004, which claims benefit of priority to provisional application 60/480,540, filed 6/20/2003. Claims 1-13, 16, 18, 20, and 22-26, as amended, are pending.

***Election/Restrictions***

1. Applicant's species election without traverse of the condition endometriosis; the COX-2 inhibitor etoricoxib; the oral contraceptive norethindrone; and the GnRH-agonist leuprolide acetate; in the reply filed on 2/12/2009 is acknowledged.

2. Claims 13, 18, and 20 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 2/12/2009.

***Priority***

3. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. The instant claims are supported by the disclosure of provisional application 60/480,540, and therefore are entitled to an effective filing date of 6/20/2003.

***Information Disclosure Statement***

4. The information disclosure statement (IDS) submitted on 12/7/2005 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement has been considered by the examiner.

***Claim Objections***

5. Claim 11 is objected to because of the following informalities: "post-menapausal" is misspelled. Appropriate correction is required.

***Claim Rejections - 35 USC § 102***

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 1-11 are rejected under 35 U.S.C. 102(b) as being anticipated by Masferrer et al. (WO98/22101, published 5/28/1998, supplied by Applicant on the IDS dated 12/7/2005), as evidenced by Bulun et al. (J. Mol. Endocr. 25, 35-42, 2000, supplied by Applicant on the IDS dated 12/7/2005).

Masferrer et al. teach a method of treating or preventing disorders of the female reproductive system including endometriosis, in a human subject in need of such treatment or prevention, by administering a therapeutically effective amount of a cyclooxygenase-2 (COX-2) inhibitor (p. 3, line 13 to p. 4, line 37; see especially claim 3,

"wherein the angiogenesis-related disorder is endometriosis"; see also pages 5-17 where various "selective" COX-2 inhibitors are disclosed), which reads on claim 1. Further, since Masferrer et al. teach methods of administering COX-2 inhibitors to treat or prevent disorders dependent on the angiogenic process by inhibiting angiogenesis, this reads on methods of retarding, preventing, reversing, and reducing [the] number or severity of the development of endometriotic lesions as recited in claims 2, 3, 4, and 5, respectively.

While Masferrer et al. do not explicitly teach the administration of COX-2 inhibitors to inhibit or reduce elevated levels of aromatase, this occurs inherently whenever a COX-2 inhibitor is administered to a patient with endometriosis. As taught by Bulun et al., prostaglandin E2 (PGE2) is the most potent inducer of aromatase activity in endometriotic stromal cells, and estrogen increases PGE2 formation by stimulating the COX-2 enzyme, setting up a positive feedback loop that COX-2 inhibitors would necessarily disrupt, inhibiting and reducing levels of PGE2 and in turn aromatase in endometriotic implants (p. 37, col. 1 and Fig. 2). Because estrogen promotes this process, such endometriotic lesions would be expected to be responsive to hormonal therapy (for example, by the administration of antigonadotropin or antiestrogen agents), which reads on methods of retarding, preventing, and reversing the development of endometriotic lesions of a type amenable to hormonal therapy, as recited in claims 6, 7, and 8, respectively. In addition, Masferrer et al. teach the administration of COX-2 inhibitors to patients in need of angiogenesis inhibition (p. 3, line 32), which would include patients at risk of having endometriotic lesions, as recited

by claims 9 and 10, and patients with post-menopausal endometriosis, as recited by claim 11. See *In re Schreiber*, 128 F.3d 1473, 1478, 44 USPQ2d 1429, 1432 (Fed. Cir. 1997) ("[C]hoosing to define an element functionally, i.e., by what it does [e.g., retarding endometriotic lesions], carries with it a risk...[W]here the Patent Office has reason to believe that a functional limitation asserted to be critical for establishing novelty in the claimed subject matter may, in fact, be an inherent characteristic of the prior art, it possesses the authority to require the applicant to prove that the subject matter shown to be in the prior art does not possess the characteristic relied on."); see also *In re Spada*, 911 F.2d 705, 708, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990); see also *In re Best*, 562 F.2d 1252, 1254-55, 195 USPQ 430, 433-34 (CCPA 1977). Further, the fact that Masferrer may not have fully appreciated these claimed functions (e.g., retarding lesions) is of no moment. See *MEHL/Biophile Int'l Corp. v. Milgraum*, 192 F.3d 1362, 1366, 52 USPQ2d 1303, 1307 (Fed. Cir. 1999) ("Where, as here, the result is a necessary consequence of what was deliberately intended, it is of no import that the article's authors did not appreciate the results."); *In re Woodruff*, 919 F.2d 1575, 1578, 16 USPQ2d 1934, 1936 (Fed. Cir. 1990) ("It is a general rule that merely discovering and claiming a new benefit of an old process cannot render the process again patentable.").

***Claim Rejections - 35 USC § 103***

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 12 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Masferrer et al. (WO98/22101, cited above) in view of Riendeau et al. (J. Pharm Exp. Ther. 296(2), 558–566, 2001).

Masferrer et al. teach a method of treating or preventing disorders of the female reproductive system such as endometriosis, in a human subject in need of such treatment or prevention, by administering a therapeutically effective amount of a cyclooxygenase-2 (COX-2) inhibitor (p. 13, line 13 to p. 4, line 37). While Masferrer et al. teach a wide array of COX-2 selective inhibitors, they do not teach the specific compound etoricoxib.

Riendeau et al. teach etoricoxib as a novel COX-2 inhibitor with 106-fold selectivity in human whole blood assays *in vitro* and with the lowest potency of inhibition of COX-1 compared with other reported selective agents (abstract), the administration of which in the treatment or prevention of endometriosis meets the limitations as recited in claims 12 and 16.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use etoricoxib as taught by Riendeau et al. in the method of Masferrer et al. for the treatment of endometriosis. A person of ordinary skill in the art would have been motivated to use this more "selective" COX-2 inhibitor like etoricoxib in order to avoid the bad side effects that are known to be associated with the inhibition of COX-1 (e.g., see Masferrer et al., page 5, lines 18-23, "the use of

cyclooxygenase-2 selective inhibitors is highly advantageous in that it minimize[s] the gastric side effects that can occur with non-selective NSAIDs [i.e., compounds that inhibit COX-1]"). In addition, a person of ordinary skill in the art would reasonably have expected to be successful because Masferrer et al. teach that any COX-2 inhibitor can be used to effectively treat endometriosis, which would encompass Riendeau's entoricoxib. In addition, as recognized by MPEP §2144.06, it is *prima facie* obvious to substitute art-recognized equivalents, and an express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. *In re Fout*, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). Here, Riendeau et al. expressly states that etoricoxib is an art-recognized selective COX-2 inhibitor equivalent (e.g., see abstract wherein etoricoxib is compare to other known COX-2 "equivalents" like rofecoxib, valdecoxib, etc.).

10. Claims 22, 23, 25, and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Masferrer et al. (WO98/22101, cited above) in view of Heinrichs (US Pat. 6,265,393, issued 7/24/2001).

Masferrer et al. teach a method of treating or preventing disorders of the female reproductive system such as endometriosis, in a human subject in need of such treatment or prevention, by administering a therapeutically effective amount of a cyclooxygenase-2 (COX-2) inhibitor (p. 13, line 13 to p. 4, line 37). While Masferrer et al. teach the administration of a wide array of COX-2 selective inhibitors, they do not teach the concomitant or sequential co-administration of an oral contraceptive.

Heinrichs teaches a method of prophylactic treatment and prevention of endometriosis symptoms (col. 4, lines 15-39) by the administration of a gonadotropin-releasing hormone (GnRH) agonist such as leuprolide acetate to induce oligomenorrhea or amenorrhea (col. 9, lines 30-35), followed by the co-administration of an estrogen agent and a progestin agent such as norethindrone. (col. 8, lines 30-45; Table 2).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to employ the compounds of Heinrichs in the methods of Masferrer et al. One of ordinary skill in the art would have had an expectation of success in the treatment or prevention of endometriosis by the concomitant co-administration of the oral contraceptive norethindrone with a COX-2 inhibitor, as recited by claims 22 and 23, because chronic pain is a significant symptom of endometriosis, COX-2 inhibitors are NSAID analgesics, and the concomitant co-adminstration of norethindrone with another active agent to prevent the symptoms of endometriosis was known. For the same reasons, one of ordinary skill in the art would have had an expectation of success in the treatment or prevention of endometriosis by the sequential co-administration of the GnRH agonist leuprolide acetate with a COX-2 inhibitor, as recited by claims 25 and 26, because the sequential co-administration of leuprolide acetate with another active agent to prevent the symptoms of endometriosis was known. Further, a person of ordinary skill in the art would be motivated to use this COX-2 inhibitor to lesson the pain associated with endometriosis.

In addition, according to MPEP §2144.06, "[i]t is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same

purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980). Here, both the COX-2 inhibitor of Masferrer et al. and the GnRH agonist combination of Heinrichs have been shown to be useful for the same purpose (i.e., treatment of endometriosis). Thus, a third combination employing both the COX-2 inhibitor and the GnRH agonist combination would likewise be obvious.

11. Claim 24 is rejected under 35 U.S.C. 103(a) as being unpatentable over Masferrer et al. (WO98/22101, published 5/28/1998, cited above).

Masferrer et al. teach a method of treating or preventing disorders of the female reproductive system such as endometriosis, in a human subject in need of such treatment or prevention, by administering a therapeutically effective amount of a cyclooxygenase-2 (COX-2) inhibitor (p. 13, line 13 to p. 4, line 37). In addition, Masferrer et al. also teach that COX-2 selective inhibitors are a class of nonsteroidal anti-inflammatory drugs (NSAIDs) which inhibit the production of prostaglandins, thereby reducing pain, swelling, and inflammation (p. 1, line 18 to p. 2, line 5).

While Masferrer et al. do not teach the specific timing of the administration of COX-2 selective inhibitors, i.e., perioperatively or post-surgically as recited by claim 24, the Examiner takes official notice that it is well-known in the art that (a) all surgical procedures result in pain and inflammation, and (b) the administration of NSAIDs is effective in reducing pain and inflammation. One of ordinary skill in the art would have

been motivated to administer a COX-2 inhibitor in connection with an endometrial surgical procedure to treat pain, because any type of surgery results in pain and inflammation, and COX-2 inhibitors are commonly known in the treatment of pain associated with surgery.

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to administer a COX-2 selective inhibitor perioperatively or as a post-surgical therapy because there would have been a reasonable expectation of success treating the same patient population for pain associated with endometrial surgery by administering a COX-2 selective inhibitor.

***Conclusion***

12. Claims 1-12, 16, and 22-26 are rejected.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to SARA E. CLARK whose telephone number is (571) 270-7672. The examiner can normally be reached on Mon - Thu, 7:30 am - 5:00 pm (EST). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Patrick J. Nolan can be reached on 571-272-0847. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

SEC

/Patrick J. Nolan/
Supervisory Patent Examiner, Art Unit 4121